Claim Rejections Under 35 USC §§ 102(b) and 103

Claims 13-29 were rejected as being anticipated by **Larrson *et al.*, WO 96/02535** (Applicants' cited Reference BA) and also as being unpatentable over **Von Unge, WO 97/02261** (Applicants' cited Reference BC).

Dealing with the allegedly anticipatory reference first, Applicants do not dispute the Office's position that the reference teaches a method for the enantioselective production of the enantiomers of lansoprazole; in fact, Applicants specifically disclosed and incorporated by reference, **Larsson** into the present specification at page 6, last sentence, last paragraph. However, a method for the stereoselective production of the individual enantiomers of lansoprazole is not the subject of Applicants' claims.

The invention disclosed and claimed by the present Applicants concerns various embodiments of methods of treating ulcers, gastroesophageal reflux disease, psoriasis, as well as various conditions caused by or contributed to by gastric hypersecretion, which involve the administration of a therapeutically effective amount of optically pure *S*(-)lansoprazole. There is no disclosure in **Larsson** of such methods. The only statement within **Larsson** that relates to the treatment of a disease state in a human is found at page 1, last line, first paragraph and again in claim 34, is an entirely generic statement that the single enantiomeric compounds prepared by the **Larsson** method may be used in medicine.

There is no discussion, comment, teaching or disclosure in **Larsson** of what disease states would benefit from the administration of the compounds, and as such, the reference does not support a §102(b) rejection of the claims, and Applicants respectfully request that the rejection be withdrawn.

Turning now to **Von Unge**, it is the Office's position that this reference teaches a method for the optical purification of the single lansoprazole enantiomers, and because the racemic lansoprazole compound is known to be effective as a gastric acid secretion inhibitor, it would have been obvious to one of skill to produce the single enantiomers and use one or the other in the treatment of ulcers and other digestive problems caused by excess gastric acid secretion.

Once again, Applicants do not contest the Office's position that **Von Unge** discloses a method for the optical purification of the individual lansoprazole enantiomers (as with **Larsson** above, Applicants also specifically disclosed **Von Unge** in the present specification at page 6, first sentence, last paragraph.

Although **Von Unge** makes no specific statement or reference to the use of the single lansoprazole enantiomers (as opposed to the racemate) for the treatment of the disease states as claimed by Applicants. Instead, the Office relies solely on a holding of *prima facie* obviousness based upon **Von Unge**'s statement at page 2, lines 14-16 that the "single enantiomers of pharmacologically active compounds have met an increased interest in the last years because of improved pharmacokinetic and biological properties."

While this statement may be true, Applicants respectfully disagree that the statement, when considered in the context of the state of the art at the time of Applicants' discovery, does not support a *prima facie* holding of obviousness. As support for their position, Applicants offer the following remarks.

First, while **Von Unge** alleges a priority date of July 3, 1995 (the allegedly anticipatory reference **Larsson** alleges a priority date of July 15, 1994), as of Applicants' earliest disclosure date January 30, 1998 (filing date of US Provisional Application 60/073,141), lansoprazole was commercially available only as the 1:1 racemic mixture (PREVACID®, TAP Pharmaceuticals, Inc., Lake Forest, IL USA). In fact, PREVACID® remains the only commercially available

lansoprazole product to date, and Applicants are not aware of any reports or disclosures that would indicate that any person of skill had been motivated by **Von Unge** to synthesize one or both of the optically pure isomers of lansoprazole and test their therapeutic activity in the treatment of the various gastric conditions involved in Applicants' claims.

Secondly, as indicated by the enclosed reference: Arimori, K *et al.*, "Pharmacokinetic Differences Between Lansoprazole Enantiomers in Rats," *J. Pharm. Pharmacol.*, 50:1241-45 (1998; accepted for publication July 5, 1998), the state of the art subsequent to Applicants' priority date regarding the potential for differences in the pharmacological activities of the individual lansoprazole enantiomers remained uncertain:

> . . . Lansoprazole has an asymmetric sulphur in the chemical structure and is administered clinically as a racemic mixture of the (+) and (-) enantiomers. . . . Because limited information is available about potential differences between the pharmacokinetics and pharmaco-dynamics of the enantiomers of lansoprazole (emphasis added) (page 1241, paragraph bridging columns 1 and 2)

According to **Nagaya** (Applicants' cited Reference CA), which reported the results of a study comparing the effects of the two single enantiomers on ($H^+ + K^+$)-ATPase activity in canine gastric microsomes and on acid formation in canine parietal cells, "the two enantiomers inhibited ($H^+ + K^+$)-ATPase in gastric microsomes with almost the same potency" and that "the effects of the (+) and (-) enantiomers of lansoprazole on acid formation stimulated by db-cAMP in isolated parietal cells were almost identical," (page 1878, column 1, first and second paragraphs, respectively), whereby they concluded that "the actions of the two enantiomers are considered to be **identical** in the two assay systems" (page 1877, column 2, first paragraph) and therefore, "[f]rom these results it is suggested that both enantiomers of lansoprazole have antisecretory action due to the inhibition of (H^+ and K^+)-ATPase and that **the inhibitory effects of the two enantiomers are almost the same** . . ." (page 1878, column 1, last paragraph).

Nagaya, H. *et al.*, "Effects of the Enantiomers of Lansoprazole (AG-1749) on ($H^+ + K^+$)-ATPase Activity in Canine Gastric Microsomes and Acid Formation in Isolated Canine Parietal Cells," *Biochemical Pharmacology*, 42:1875-78 (1001).

Thus, because the state of the art at the time of the invention was such that the person of skill would have believed that the two enantiomers provided nearly identical inhibitory activity, there would have been no motivation to undertake the time and expense to pursue the separation and purification of either enantiomer for its individual administration. This is clearly supported by the fact that lansoprazole remains commercially available only as a racemic mixture. Notwithstanding the lack of motivation to do so, in addition to the expenditure of time, resources and personnel required to pursue the separation, purification and testing of one or both of the lansoprazole enantiomers, Applicants have done just that, and have discovered significant advantages associated with the administration of the optically pure *S*(-)-enantiomer.

Referring to their specification, Applicants report that:

> It has now been discovered that the optically pure (-) isomer of lansoprazole is a superior agent for treating ulcers of the stomach, duodenum and esophagus, gastroesophageal reflux diseases, Zollinger-Ellison Syndrome, psoriasis and other disorders, including those that would benefit from an inhibitory action on H^+, K^+-ATPase in that it provides this effective treatment while substantially reducing the adverse effects of racemic lansoprazole . . . [and] is a superior agent for treating ulcers and other disorders by virtue of its lessened liability for drug-drug interactions and its greater predictability of dosage among patients, . . . Surprisingly, it also shows a longer duration, a higher AUC (area under the curve – a composite measure of efficacy and duration), and a more rapid onset as a result of lower first pass metabolism.
> (Specification, page 7, second paragraph).

As there was no motivation at the time of the invention to undertake the separation, purification and testing of the individual lansoprazole enantiomers, despite the knowledge of one or more methods for doing so, Applicants respectfully disagree with the Office's finding of *prima facie* obviousness in view of **Von Unge**, and respectfully request that the rejection be withdrawn.

There being no further issues, the application (including claims 13-29), is believed in condition for allowance, and such action is respectfully requested.

Respectfully submitted,

October 21, 2002

Candice J. Clement

Candice J. Clement, Esq.
Attorney for Applicants
United States Registration Number 39, 946
HESLIN ROTHENBERG FARLEY & MESITI, P.C.
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579